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14. ABSTRACT
The full scope of this research is to develop a robust and reliable circadian phase estimation system, and use it for model identification and light-based control design. The objective of this project is to develop preliminary results in the following directions to lay the foundation of the full research. 1. Circadian phase estimation and control: Demonstrate the applicability of the adaptive notch filter (ANF) to extract circadian phase from noisy Drosophila locomotive activity measurements and the efficacy of using the ANF output for light based circadian phase control.

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Report Title

Final Report: Light-based Modeling and Control of Circadian Rhythm

ABSTRACT

The full scope of this research is to develop a robust and reliable circadian phase estimation system, and use it for model identification and light-based control design. The objective of this project is to develop preliminary results in the following directions to lay the foundation of the full research. 1. Circadian phase estimation and control: Demonstrate the applicability of the adaptive notch filter (ANF) to extract circadian phase from noisy Drosophila locomotive activity measurements and the efficacy of using the ANF output for light based circadian phase control. 2. Pathway to human deployment: Demonstrate the feasibility of a human wearable sensor that could be used with the ANF algorithm to extract the circadian phase of human users.

Enter List of papers submitted or published that acknowledge ARO support from the start of the project to the date of this printing. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

Received Paper

TOTAL:

Number of Papers published in peer-reviewed journals:

(b) Papers published in non-peer-reviewed journals (N/A for none)

Received Paper

TOTAL:

Number of Papers published in non peer-reviewed journals:

(c) Presentations

Number of Presentations: 0.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received Paper

TOTAL:

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received Paper

TOTAL:

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):

(d) Manuscripts

Received Paper

TOTAL:

Number of Manuscripts:

Books

Received Book

TOTAL:

Received	Book Chapter

TOTAL:

Patents Submitted

Patents Awarded

Awards

Graduate Students

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Names of Post Doctorates

NAME	PERCENT_SUPPORTED
Wei Qiao	1.00
FTE Equivalent:	**1.00**
Total Number:	**1**

Names of Faculty Supported

NAME	PERCENT_SUPPORTED	National Academy Member
John Wen	0.00	
Agung Julius	0.00	
FTE Equivalent:	**0.00**	
Total Number:	**2**	

Names of Under Graduate students supported

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period: 0.00

The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:...... 0.00

The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:...... 0.00

Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):...... 0.00

Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:...... 0.00

The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense 0.00

The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields:...... 0.00

Names of Personnel receiving masters degrees

NAME

Total Number:

Names of personnel receiving PHDs

NAME

Total Number:

Names of other research staff

NAME	PERCENT_SUPPORTED

FTE Equivalent:
Total Number:

Sub Contractors (DD882)

Inventions (DD882)

Scientific Progress

See Attachment

Technology Transfer

Award # W911NF-13-1-0265.

Project Title: Light-Based Modeling and Control of Circadian Rhythm

PI: John T. Wen, Agung Julius, Rensselaer Polytechnic Institute,

Objective:
The full scope of this research is to develop a robust and reliable circadian phase estimation system, and use it for model identification and light-based control design. The objective of this STIR grant is to develop preliminary results in the following directions to lay the foundation of the full research.
1. Circadian phase estimation and control: Demonstrate the applicability of the adaptive notch filter (ANF) to extract circadian phase from noisy *Drosophila* locomotive activity measurements and the efficacy of using the ANF output for light based circadian phase control.
2. Pathway to human deployment: Demonstrate the feasibility of a human wearable sensor that could be used with the ANF algorithm to extract the circadian phase of human users.

Approach
1. Use our existing *Drosophila* testbed which consists of twelve 32-fly boxes with regular locomotive activity measurements and blue LED control (at one-minute resolution) to generate data for the construction of the phase response curve (PRC) using the ANF algorithm to compare with known results. The ANF output will be used to control the LED to achieve desired phase shift using the optimal control algorithms that the PIs have developed.
2. Extend the ANF approach to multiple sensor measurements.
3. Develop light-based control strategy using the PRC information.

Scientific barriers
1. The Drosophila locomotive activity data is noisy and is masked by other factors such as stimulation through the visual pathway. The parameters in ANF must be tuned to balance between two competing objectives: fast response (the ANF output closely tracks the true circadian phase without excessive delays) and noise rejection (the ANF output is not overly influenced by noise and non-circadian factors).
2. The current ANF approach is based on a single sensor stream. In human deployment, wearable sensors will likely be used which could provide multiple sensor streams, such as actigraphy, heart rate, skin temperature, etc. Effective sensor fusion scheme integrating these multiple streams of sensors is currently lacking.
3. There are multiple circadian oscillator models. A model suitable for light-based control design must balance between model complexity and fidelity. Model-based control faces the issue of controlling on the unit circle S^1.

Significance

Current circadian estimation scheme is based on days of data. The ANF method could reduce the estimation delay to hours instead of days. This would allow feedback implementation of light-based circadian phase control strategy using wearable sensors. Effective circadian phase would be important for shift work hours or travel across multiple time zones.

Accomplishments

1. We have applied the phase reduction technique to circadian oscillation and came up with the first complete solution of the time optimal control problem. See Figure 1 for the structure of the feedback control, which is determined completely by the PRC (and the maximum light amplitude). Figure 2 shows the comparison between various control strategies. The optimal feedback strategy reduces entrainment time to less than a third of the periodic entrainment. The preliminary version of this work was presented at the IEEE Conference on Decision and Control in December 2013. The expanded result has been submitted to the IEEE Transaction of Automatic Control.
2. We have applied the ANF to *Drosophila* data and constructed PRC that is comparable to the result in the literature using off-line methods. The result is shown in Figure 3.
3. We have developed a multi-ANF approach to incorporate multiple sensor streams (possibly in different rates) for circadian phase estimation. The structure of the filter is shown in Figure 4. The paper has been submitted to the International Journal on Adaptive Control and Signal Processing.

Collaborations and leveraged funding

This project leverages the Lighting and Health research thrust in the Smart Lighting Engineering Research Center (SLERC) at Rensselaer Polytechnic Institute funded by the National Science Foundation. SLERC supports human circadian study with leading circadian researcher, Dr. George Brainard at Thomas Jefferson University, and the Director of the Sleep Institute at the University of New Mexico, Dr. Lee Brown. The PIs participate in this collaborative research which focuses on the human subject study.

Conclusions

This grant has allowed us to make significant progress in circadian rhythm control research. This lays a strong foundation to investigate the effect of sleep (using the two-process model) and performance.

Future plans

- Demonstrate PRC-based control for Drosophila for robust closed loop circadian rhythm entrainment.
- Develop light-based performance control by using the two-process model.

Publications:

J. Zhang, J.T. Wen, A. Julius, "Optimal and Feedback Control for Light-Based Circadian Entrainment," *Proc. IEEE Conf. Decision and Control*, Florence, Italy, 2013.

J. Zhang, W. Qiao, J.T. Wen, A. Julius, "Light-Based Circadian Rhythm Control: Entrainment and Optimization," Automatica, 68, June, 2016. pp. 44-55.

A. Julius, J. Zhang, W. Qiao, J.T. Wen, "Multi-input Adaptive Notch Filter and Observer for Circadian Phase Estimation," to appear in the International Journal on Adaptive Control and Signal Processing, 2016.

W. Qiao, J.T. Wen, A. Julius, "Entrainment Control of Phase Dynamics," to appear in IEEE Transaction on Automatic Control, April, 2017.

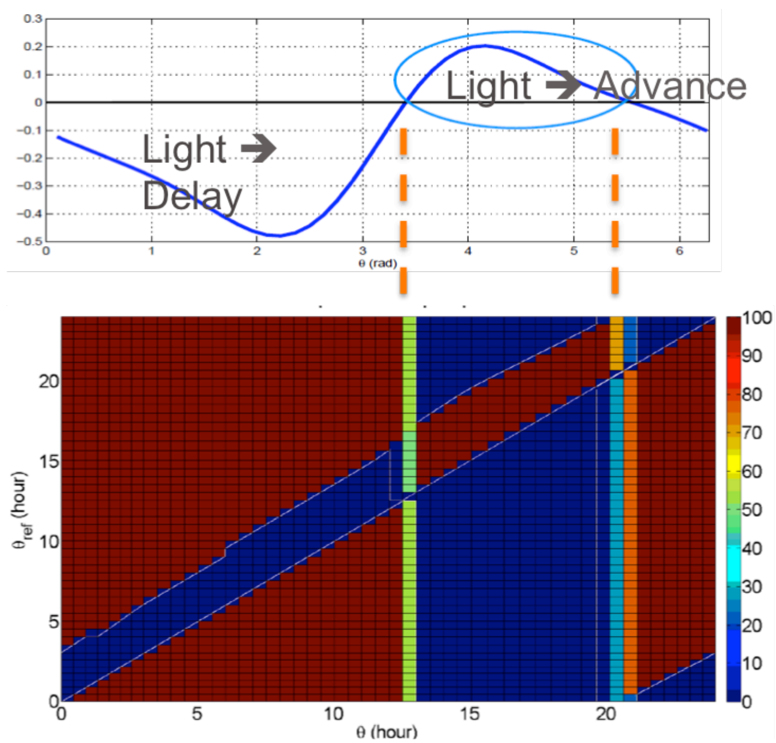

Figure 1 Feedback entrainment algorithm, determined completely by the PRC. The 3-hour switching zone is due the S^1 topology of the phase space. The algorithm is in fact optimal in terms of entrainment time.

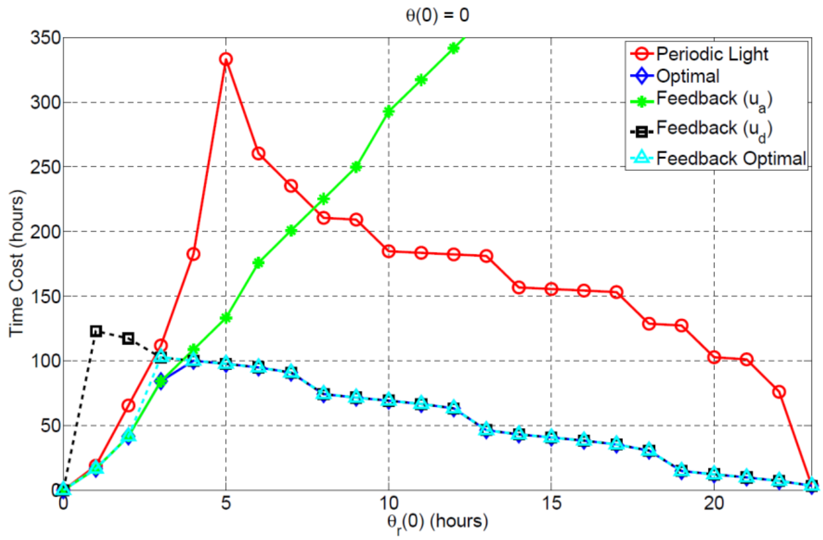

Figure 2 Comparison of optimal entrainment cost between open loop periodic entrainment (at 50% duty cycle), optimal open loop entrainment, feedback entrainment, and subtractive entrainment. The feedback entrainment is optimal, and provides additional robustness.

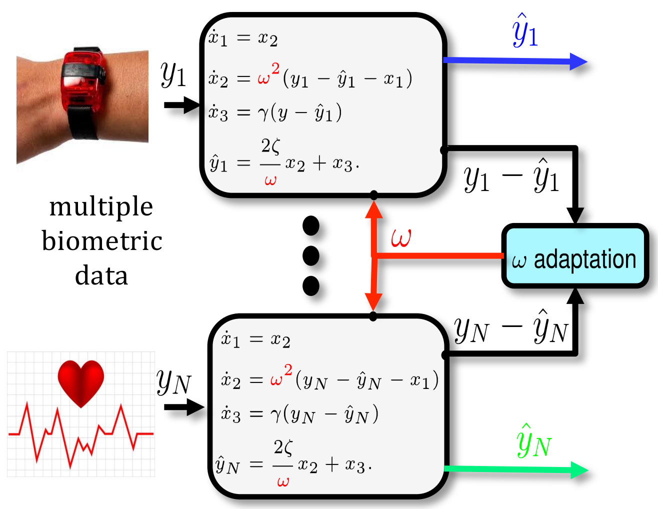

Figure 3 Extension of ANF to multiple sensor inputs

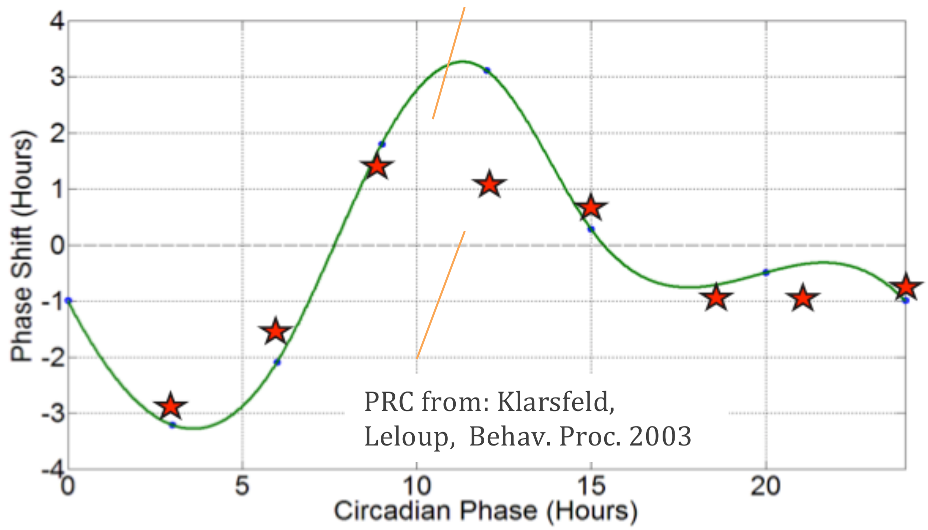

Figure 4 Phase response curve (PRC) for Canton-S strain Drosophila obtained by applying ANF to actigraphy data as compared with PRC from the literature.